Haemonetics Corporation

Presentation to the Blood Products Advisory Committee

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Thank you for the opportunity to address the committee today.

Last April, Haemonetics Corp. submitted written comments to the FDA on the draft guidance entitled "Guidance for Industry: Pre-storage Leukoreduction of Whole Blood and Blood Components Intended for Transfusion," dated January 2001. We wish to present today the major points contained in those written comments.

Product Definition

The specifications in the guidance document do not include Red Blood Cells, Pheresis, Leukoreduced. As a point of clarification, we suggest that FDA create either separate specifications for this product, or clarify that Red Blood Cells, Pheresis, Leukoreduced are included in the Red Blood Cells, Leukoreduced group.

Minimum Red Cell Volume

The specifications for Whole Blood, Leukoreduced and Red Blood Cells, Leukoreduced specify a *minimum* therapeutic content of 160 ml of red blood cells after filtration. If we assume that the "at least 85% of the original therapeutic component" remains as a specification (and we believe that it should), then the minimum therapeutic content of red blood cells prior to filtration must be 188 ml. We believe that a 450 ml unit of whole blood drawn from a donor with 38% hematocrit will most likely not meet the minimum therapeutic content of 160 ml of red blood cells after filtration. Specifically, a 450 ml whole blood unit drawn from a donor with a 38% hematocrit should yield 171 ml of red cells, and, if 85% is retained post-filtration, a leukoreduced red cell volume of 145 ml. Therefore these donors would be unable to donate Red Blood Cells, Leukoreduced under the proposed guideline.

The 20^{th} Edition of the AABB Standards defines an apheresis red cell unit as having an average red cell content of 180 ml (prior to filtration). Products containing 180 ml will most likely not meet the minimum therapeutic content of 160 ml of red blood cells post filtration, due to the losses inherent in filtration.

We suggest that the Agency modify the proposed guidelines to be consistent with the AABB standards and with other FDA standards. If this were to be the case, the minimum therapeutic content of Red Blood Cells, Leukoreduced would be

145 ml. Alternatively, the standard could be set such that the *average* content was 160 ml post-filtration.

Another option would be for the Agency could choose to adopt the red cell content standards as defined by the European Union. In these standards, Red Blood Cell products, non-leukocyte reduced, must contain a minimum of 45 g/Hg per unit (approximately 135 ml of red cell mass per unit), Red Blood Cell products, leukocyte reduced, must contain a minimum of 40 g/Hg per unit (approximately 120 ml of red cell mass per unit).

Process Validation

The guidance document specifies that each major leukocyte reduction process (filtration of Whole Blood; filtration of Red Blood Cells; filtration of Platelets; filtration of Platelets, Pheresis; direct collection of leukocyte reduced Platelets, Pheresis) should be validated initially and monitored periodically. The guidance document later specifies that "[u]sing more than one variation of filter, SOP (e.g. different temperature) or apheresis instrument increases the total number of process variations which would require initial validation and weekly evaluation; quality control should be performed separately for each of the major leukocyte reduction process variations."

We interpret this as a requirement that each leukocyte reduction process used by the blood collection facility should be validated *separately*. For example, if a blood collection facility uses two apheresis red cell collection devices from different manufacturers, and leukocyte reduces these apheresis red cell products using an in-line filter for one group of the collected products, and uses two different filters connected by SCD for the second group of the collected products, the draft guidance would require that the blood center validate these three processes separately, although they all fall into the category of filtration of RBCs. Is this the intent? We suggest that process validation requirements be more explicitly defined in the guidance document.

Further to this point, if establishing a separate validation process for each leukocyte reduction process used is indeed the intent of the document, we wish to point out that this approach is inconsistent with the quality control requirements contained in the FDA Guidance "Recommendations for Collecting Red Blood Cells by Apheresis Methods." This guidance requires a fixed number of apheresis red blood cell products be validated initially and monitored periodically for the overall apheresis red blood cell manufacturing process (*independent from the device, manufacturer, or collection protocol used)*. The actual number of procedures tested for each combination of procedure used by the blood center within this fixed number is based upon the actual collection distribution implemented at the blood center.

We believe that this approach is more reasonable given the philosophy of not unnecessarily burdening blood centers. We suggest that the FDA incorporate the quality monitoring approach of the red cell apheresis guidance into the guidance for leukoreduction of whole blood and blood components.

The guidance document further proposes that blood centers test "60 consecutive units for each of the [..] major process variations" to conduct the initial process validations. As we stated above, this approach is inconsistent with the approach posed in the Red Cell Apheresis Guidance, where initial process validation involves evaluation of 100 consecutive units to validate *the entire apheresis red blood cell collection process (regardless of device, manufacturer, or collection protocol used)*, with a 95% pass rate.

After completion of the initial validation, the Agency proposes that "[t]he minimum number of products tested for each type of product and process should be 20 per month." Our concern is the same as we stated with respect to initial process validation, i.e., is the guidance requiring that each leukocyte reduction process used by the blood collection facility should be monitored separately on a monthly basis? For example, if a blood center uses five different leukocyte reduction processes for RBCs, the guidance would require it to monitor 100 units per month (5 leukoreduction processes x 20 units per month). Again, this is inconsistent with the approach used in the Red Cell Apheresis Guidance, where monthly QC involves evaluation of 50 units to monitor the entire apheresis red blood cell collection process with a 95% pass rate.

The guidance document proposes that the initial validation "testing of 60 units (with all units acceptable) should be repeated whenever an unacceptable unit is identified or a leukocyte reduction process is significantly changed." The rationale is that "[w]hen an unacceptable unit is detected, the minimum process standard (more than 95% of units acceptable, at the 95% confidence level) is no longer assured." Does this mean that the initial validation testing be repeated every *single* time a unit fails the leukocyte reduction process criteria, even if the cause of the failure can be readily identified and results from a "one-time event"? We believe that this would be an unreasonable burden. For a clearly identified isolated incident, not related to process control or process failure, validation testing should not be repeated.

We thank the members of the Blood Products Advisory Committee for their attention.